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(54) Title: HEDGEHOG-RELATED PROPHYLAXIS, THERAPY AND DIAGNOSIS OF GI TRACT CARCINOGENESIS

(57) Abstract: The present invention is based on the key roles played by Hedgehog proteins in the regulation of homeostasis of the adult intestinal epithelium. Ihh is expressed in the adult mammalian colon and provides a lineage-instructive signal and regulates colonic epithelial morphogenesis in a compartmental fashion. Loss of Ihh expression precedes morphological change in colon tumorigenesis, i.e. carcinogenesis, and Ihh was absent in HT-29 colon carcinoma cells. Treatment of cancerous HT-29 cells with exogenous Hedgehog protein restored their differentiation. Ihh thus plays a pivotal role in the maintenance of colonic epithelial homeostasis in the differentiation of the GI tract cells and is essential for the enrolment of these GI tract cells on the Death program thus maintaining homeostasis to avoid or treat carcinogenesis. In addition, in gastric cancer expression of Shh is lost and loss of Shh expression precedes morphological changes in the parietal cells of the stomach. Shh is specifically expressed in fundic glands as well as in gastric heterotopia in the esophagus in Meckel's diverticulum. Shh thus has a unique role as a morphogen in fundic gland homeostasis. The present invention relates to methods in which a source of Hedgehog proteins is used prophylactically or therapeutically to maintain homeostasis of the adult intestinal epithelium. In particular the invention relates methods whereby sources of Hedgehog protein are used to prevent or treat carcinogenesis in adult gastric and colonic tissues. The invention also relates to Hedgehog-based method of diagnosing susceptibility for or the presence of carcinogenesis in the adult GI tract, particularly in gastric and colonic tissues. The invention further provide for compositions to be used in the Hedgehog-based methods of diagnosing, preventing and treating epithelial tumorigenesis in the adult GI tract.

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